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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/042,141	01/11/2002	Steven M. Ruben	PZ040P1C1	7361

22195 7590 02/19/2004

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EXAMINER	
SPIEGLER, ALEXANDER H	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 02/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/042,141	RUBEN ET AL.	
	Examiner	Art Unit	
	Alexander H. Spiegler	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,11-16,19,20,22 and 24-55* is/are pending in the application.

4a) Of the above claim(s) *1,2,13-15,19,20 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,12,16 and 24-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/08/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. This action is in response to Applicant's response, filed on December 8, 2003. Currently, Claims 1-2, 11-16, 19-20, 22 and 24-55 are pending, Claims 1-2, 13-15, 19-20 and 22 have been withdrawn as being drawn to a non-elected invention (see MPEP § 821), and Claims 11-12, 16 and 24-55 are rejected herein.

Election/Restrictions

2. Applicant's election with traverse of Group II (directed to polypeptides, which corresponds to Claims 11-12, 16 and 24-55) the polypeptide of SEQ ID NO: 48, and clone ID HKAOV90 are acknowledged.

Applicants traversal is on the ground(s) that Groups I-X are directed to subject matter that is closely interrelated and therefore examination of all of the groups would not place an undue burden on the Examiner. This is not found persuasive because it is maintained that undue burden would be required to examine the claims of Groups I-X. Restriction of related inventions is proper if it can be shown that the inventions have a different classification, or have acquired a separate status in the art or have a different field of search (see MPEP 808.02). The claims of groups I-X have acquired a separate status in the art as recognized by their different classification and as recognized by their divergent subject matter. A search of the distinct inventions would not be co-extensive as evidenced by the requirement for searching different keywords, by the different classification of each invention, and because a sequence search for nucleic acids and polypeptides (for example) requires a different structural search, as a nucleic acid search requires the search of nucleotides, whereas a polypeptide search requires the search

of amino acids. Currently, databases for nucleic acids and polypeptides each contain hundreds of thousands of sequences, and therefore, searching more than a single nucleic acid or polypeptide sequence is a serious burden for the Office. Furthermore, it is maintained that each of the inventions are distinct for the reasons discussed in the previous Office action. Accordingly, because undue burden would be required to examine each of the claimed inventions, the requirement is still deemed proper, and is therefore maintained.

However, as Applicants point out, rejoinder of Claims 14-15 will be permissible if the claims of Group II are found to be allowable.

Priority

3. Applicants' claim to priority under 35 U.S.C. 119 and 120 is acknowledged.

CRF/Sequence Notes

4. The Sequence Listing filed in this application complies with the requirements of 37 CFR 1.821-1.825 and has been entered.

Specification

5. The disclosure is objected to because the title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 11-12, 16 and 24-55 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility.

The specification teaches SEQ ID NO: 48 is the translation product of "Gene 3" (see Table 1 on page 75). Specifically, the specification teaches "the translation product of this gene shares sequence homology with Prominin, a novel microvilli-specific polytopic membrane protein of the apical surface of epithelial cells". (see page 12, lines 27-29). The specification also states, "the translation product of this gene also shares sequence homology with AC133 antigen homolog" (see page 12, lines 30-31). However, the specification does not teach what the sequence homology is between the translation product of this gene and Prominin or AC133 antigen homolog. Furthermore, the specification states, "the polypeptide of this gene has been determined to have transmembrane domains at *about* amino acid positions 154-170, 426-442, 482-498, 104-120, and 784-800", and concludes, "based upon these characteristics, *it is believed* that the protein product of this gene shares structural features to type IIIa membrane proteins" (emphasis added) (see page 13, lines 24-28). By using the term "about", it is not clear as to exactly where these domains (that are believed to share structural features to type IIIa membrane proteins) are actually located.

Next, the specification states, "this gene is expressed primarily in adenocarcinoma, and to a lesser extent in kidney tumor, primary breast cancer, kertinocyte and tonsils." (see page 14, lines 1-3). However, the specification does not teach or demonstrate any evidence of differential expression (e.g., between normal or cancer cells or tissues) or any other data that specifically correlates the expression of this gene or its translation product and any disease or condition.

Specifically, even if this gene is expressed in adenocarcinoma or tonsils, the specification does not teach whether this gene is expressed, for example, in normal epithelial cells or in cancerous tonsil tissue. Therefore, the limited expression data provided by the specification does not specifically assert, for example, that the claimed gene is only expressed in a cancer cell or tissue and not in a normal cell or tissues. That is, while the specification asserts some expression data, it is not clear whether other cells/tissues were tested, what cells/tissues were tested, whether they were diseased or normal samples, etc., and therefore, the specification does not teach a reasonable or specific correlation between the expression of the claimed gene and any condition or disease. Therefore, the skilled artisan would have to carry out further research to identify or reasonably confirm a "real world" context of use of the claimed sequence. Furthermore, the assertion that the gene is expressed "to a lesser extent" is also vague, since it is not clear as to what "a lesser extent" actually means or what standard this is being compared to, let alone whether expression "to a lesser extent" is significant for screening/assayable purposes.

Given the limited expression data, the specification states,

> "polynucleotides and polypeptides of the invention...are useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions such as cancer (particularly adenocarcinomas, cancers of the kidney, breast, skin and oral cavity)"

(see page 14, lines 4-7).

The asserted utility of using polynucleotides or polypeptides for diagnosis of cancer (particularly adenocarcinomas) would not be considered to be a specific utility, since there are many different types of adenocarcinomas and cancers (see for example, the NCBI MeSH search for "adenocarcinoma"). Accordingly, because the utility of diagnosing "cancer" and "adenocarcinomas" using would apply to a broad class of the invention (i.e., polypeptides) this

utility would not be consider to be a specific utility. See MPEP 2107.01 and the Utility Guidelines.

Additionally, the asserted utilities on page 14, lines 4-7, would not be considered to be substantial utilities, since the skilled artisan would have to carry out further research to identify or reasonably confirm a "real world" context of use, e.g., diagnosis a specific adenocarcinoma, or oral cavity disease or disorder, etc., in light of the specification's lack of evidence regarding any reasonable or specific correlation between the expression of the claimed gene and any disease and/or disorder. See MPEP 2107.01 and the Utility Guidelines.

Given the limited teachings in the specification, the further research required for identifying or reasonably confirming a "real world" context of use can be demonstrated by the art of Fargeas et al. (The Journal of Biological Chemistry (2003) 278(10): 8586-8596, cited in the IDS). It is preliminarily noted that in Applicants' response, Applicants acknowledge that Fargeas teaches the instant invention (SEQ ID NO: 48), stating "the present invention (now know in the art as Prominin-2)" (see page 8).

Fargeas teaches the characterization of Prominin-2, performing experiments comprising extensive expression analysis, and makes several significant findings regarding Prominin-2's expression. Specifically, Fargeas teaches examining the relative abundance of Prominin-2 mRNA "in 76 different human tissues and tumor cell lines using a multiple tissue expression array (Fig. 7A)." (page 8591, 2nd column and Figure 7) From this expression analysis, Fargeas teaches Prominin-2 was strongly expressed in adult kidney, and Prominin-2 mRNA was also detected all tissues of the digestive tract, prostate, trachea, salivary gland, thyroid glad, mammary gland, and placenta (page 8591, 2nd column and Figure 7).

Fargeas further concludes, "*No expression was evident in any of the eight tumor cell lines.*" (emphasis added) (see page 8591, 2nd column and Figure 7). Specifically, the tumor cell lines referred to include promyelotic leukemia, HeLa, chronic myelogenous leukemia, lymphoblastic leukemia, Burkitt's lymphoma, colorectal adenocarcinoma and lung carcinoma (see Figure 7). Thus, Fargeas concluded no expression was evident in several cancer cell lines, including colorectal adenocarcinoma. Fargeas demonstrates not only the level of experimentation required by the skilled artisan to identify or reasonably confirm a "real world" context of use, but that the claimed invention was not expressed in several cancer cell lines, including colorectal adenocarcinoma. Accordingly, given the lack of evidence regarding any reasonable or specific correlation between the expression of the claimed gene or its polypeptide, and any disease and/or disorder, in light of the detailed experimentation and negative teachings of Fargeas with respect to Prominin-2's expression in cancer cell lines, the asserted utilities lack a substantial utility.

The specification also states, "Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for differential identification of the tissue(s) or cell type(s)." (see page 14, lines 8-10) This asserted utility is not considered to be specific because no specific target is disclosed (see MPEP 2107.01).

The specification states further,

> For a number of disorders of the above tissues or cells, particularly of the immune...and digestive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., kidney...and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

(see page 14, lines 10-16). However, the specification does not teach whether the increased or decreased expression of this gene is detected in a specific disorder relative to the standard expression level in healthy tissue or bodily fluid from an individual not having the disorder. Thus, this passage does not define a substantial utility, as the skilled artisan would have to experiment to find a correlation between the claimed gene and a disease or disorder. See MPEP 2107.01.

On page 14, line 29 to page 15, line 1, the specification states,

> The tissue distribution in adenocarcinoma, kidney tumor and breast cancer and homology to the membrane protein Prominin that the protein product of this clone would be useful in diagnosis, intervention, and treatment of tumors, especially adenocarcinoma, as well as cancers of other tissues where expression has been indicated.

This assertion also lacks a substantial utility for several reasons. First, no homology data, nor tissue distribution is present in the specification, except for the assertion that this gene is "expressed primarily" in adenocarcinoma and to "a lesser extent" in kidney tumor, etc. without providing a standard for determining when a gene is considered to be "expressed primarily" or expressed "to a lesser extent" or any data regarding expression of normal samples. Second, the specification does not provide any comparative expression data of normal or diseased samples of the claimed gene. Finally, the skilled artisan would have to carry out further experimentation to correlate expression of the claimed gene and disease. (see above)

The specification then goes on to list a laundry list of diseases and conditions (including kidney stones and AIDS, for example) that the claimed polypeptide can allegedly be use in diagnosing or treating. This assertion also lacks a substantial utility, as the skilled artisan would have to carry out further experimentation to correlate expression of the claimed gene and disease, absent any guidance from the specification. (see above).

Finally, the specification states, "Protein...may show utility as tumor markers and/or immunotherapy targets for the above listed tissues." (page 16, lines 7-9). Again, as stated above, this assertion lacks, at least, a substantial utility, as the specification does not specifically or reasonably correlate Gene 3 (or its translation product), and any disease or condition. Therefore, the skilled artisan would have to carry out further experimentation to determine what tumor or immunotherapy target the translation products of Gene 3 can be used for.

Based on the foregoing analysis, the claimed invention is not supported by either a specific or substantial utility, or alternatively, a well-established utility, as the specification does not teach a specific or reasonable correlation between the gene (or its translation product) and any specific biological activity or use in disease/disorder detection or treatment.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 11-12, 16 and 24-55 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility, or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claims 11-12 and 36-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 11-12 and 36-55 are directed to isolated proteins which are at least 90-95% identical to SEQ ID NO: 48, proteins "consisting of at least" (or comprising) 30 or 50 contiguous amino acid residues of SEQ ID NO: 48, and variants of SEQ ID NO: 48. Claims reciting 90% and 95% sequence identity are inclusive of sequences from other species, mutated sequences, and allelic variants having different functional activities than that of the protein in SEQ ID NO: 48. Claims drawn to proteins "consisting of at least" (i.e., comprising) any 30 or 50 contiguous amino acid residues of SEQ ID NO: 48, includes a large genus of proteins, having unique functional activities, whereas applicants only disclose one member of the genus (i.e., SEQ ID NO: 48) and haven't disclosed any other proteins having portions of SEQ ID NO: 48. In addition, proteins having any 30 or 50 residues of SEQ ID NO: 48 would be expected to have unique functional activities, wherein the specification has not disclosed any proteins having functional activities different from those of SEQ ID NO: 48. Furthermore, with respect to Claims 11-12, variants of SEQ ID NO: 48 encompasses thousands of possible permutations of SEQ ID NO: 48, wherein Applicants have not disclosed any variants (e.g., allelic variants) of SEQ ID NO: 48, or any functional properties of any possible variants of SEQ ID NO: 48. None of the sequences encompassed by the claimed genus meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claims.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was

in *possession* of the invention. The invention is, for purposes of the written description inquiry, *whatever is now claimed* (See page 1117)." The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed (See *Vas-Cath* at page 1116)."

The skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

> To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In *re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.
>
> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 11-12 and 16 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11-12 and 16 are indefinite because they are drawn to polypeptides that are not defined. For example, Claims 11-12 are drawn to polypeptides of SEQ ID NO: Y or the encoded sequence included in ATCC Deposit No: Z, wherein Y and Z are defined. The claims have been interpreted as Y being drawn to SEQ ID NO: 48.

Conclusion

13. No Claims are allowable.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alexander H. Spiegler whose telephone number is (571) 272-0788. The examiner can normally be reached on Monday through Friday, 7:00 AM to 3:30 PM.

If attempts to reach the examiner are unsuccessful, the primary examiner in charge of the prosecution of this case, Carla Myers, can be reached at (571) 272-0747. If attempts to reach Carla Myers are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at (571) 272-0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number (703) 872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Alexander H. Spiegler
February 17, 2004

2/18/04
CARLA J. MYERS
PRIMARY EXAMINER